Rezafungin: A Novel Antifungal for the Treatment of Invasive Candidiasis

Ms. Sakshi vidhate*1, Ms. Kale Disha*2, Mr. Shravan Somani*3, Ms. Manisha Ghavte*4,
*1 Student, Pratibhatai Pawar College Of Pharmacy, Shrirampur
*2,*3, 4, Asst. Professor, Pratibhatai Pawar College Of Pharmacy, Shrirampur, Maharashtra
Corresponding Author: Ms. Sakshi vidhate*1

Abstract :
Rezafungin is an innovative echinocandin that possesses exceptional stability and solubility, as well as a distinctive long half-life, allowing for early drug exposure through once-weekly dosing. It has demonstrated comparable efficacy to other echinocandins and exhibits activity against various species of Candida and Aspergillus, including echinocandin-resistant C. auris subgroups and azole-resistant Aspergillus isolates. Clinical data available thus far indicate strong safety and promising effectiveness. The ongoing Phase III study aims to provide further evidence regarding the efficacy of rezafungin in treating candidemia and invasive candidiasis, as well as preventing invasive mycosis in recipients of blood and bone marrow transplants. As a highly promising addition to the antifungal arsenal, rezafungin's impressive half-life offers clinical opportunities such as the early discharge of stable patients and prophylactic use in immunocompromised individuals. Mucosal and invasive candidiasis can pose challenges due to drug intolerance, antifungal resistance, drug interactions, or the host's immune status. Therefore, the development of antifungal drugs with novel mechanisms of action and significant pharmacokinetic/pharmacodynamic properties has become increasingly important. Rezafungin, with its high tissue penetration and extended half-life, provides a convenient once-weekly treatment option, eliminating the need for a central line in the management of invasive candidiasis. Additionally, Ibrax Fingop, an orally active glucan synthase inhibitor, specifically targets most echinocandin-resistant Candida species. It is currently approved for the treatment of acute vulvovaginal candidiasis and is under investigation for oral antifungal therapy following initial treatment.
Keywords : Rezafungin; invasive fungal infections; Candida; Aspergillus;

Introduction :

Candida infection:

In North America and Europe, candida yeasts are the primary cause of fungal infections. The human skin and stomach harbor commensal flora, including Candida spp. These yeasts can lead to localized illnesses, such as invasive infections in individuals with weakened immunity or breaches in mechanical barriers (such as intravascular catheters or complex abdominal surgery), as well as vulvovaginal or oral/esophageal candidiasis. The term "invasive candidiasis" (IC) encompasses both non-candidemia deep-seated candidiasis, such as intra-abdominal candidiasis (IAC) or chronic disseminated (hepatosplenic) candidiasis, and candidemia, which refers to bloodstream infections. IC can affect critically ill individuals who may appear to have a normal immune system, as well as those with compromised immunity (such as neutropenic patients). It plays a significant role in sepsis associated with healthcare, particularly in intensive care units (ICUs). The most prevalent pathogenic species of Candida in humans is Candida albicans, followed by Candida glabrata and other non-albicans Candida species (such as C. parapsilosis, C. tropicalis, and C. krusei). One recently discovered candida species is Candida auris.

Current Gaps for the Treatment of Invasive Candidiasis

The limitations of the three antifungal drug classes currently used for IC can be attributed to various factors. Firstly, the causative agents may exhibit multiple resistance, making it difficult to effectively treat the infection. Secondly, there are pharmacologic considerations, such as poor penetration of these drugs in certain tissues like the brain and eyes. Lastly, there is a risk of toxicity or drug-drug interactions associated with these medications. Echinocandin and azole-resistant Candida glabrata and Candida auris pose a fundamental problem due to their multiple resistance to at least two classes of antifungal medications. Echinocandins, in particular, have limited pharmacologic characteristics as they do not penetrate well in the kidneys, central nervous system (CNS), and eyes. Additionally, their oral bioavailability is lacking. Furthermore, the use of azoles may be restricted due to potential drug-drug interactions and harm to the liver, especially when medications that disrupt cytochrome P450 are involved. Currently, azoles are the only antifungals with oral bioavailability. Amphotericin B formulations have their own drawbacks, including nephrotoxicity and the absence of an oral formulation. To address these limitations, new antifungal medications are needed. These compounds should ideally have a wide tissue distribution, including sanctuary sites like the CNS and deep abscesses. They should also have broad-spectrum efficacy against Candida spp., even those with azole and/or echinocandin resistance. Furthermore, these medications should be available in both intravenous and oral formulations The Candida genus consists of over 200 species, many of which are part of the normal microbial population on the skin, gastrointestinal tract, and vaginal flora of humans. Candida species can cause a wide range of infections, from localized mucosal diseases to deep-seated invasive infections and candidemia. Approximately 90% of these infections are caused by Candida albicans, Nakaseomyces glabrata (previously known as Candida glabrata), Candida parapsilosis, Candida tropicalis, and Pichia kudriavzevii. Candida albicans remains the most common species responsible for candidiasis, but there has been a steady increase in the prevalence of non-albicans Candida species infections in recent years. Unlike C. albicans, non-albicans species show varying susceptibility to antifungal agents, while C. auris has emerged as a multidrug-resistant species associated with outbreaks in healthcare settings. The current antifungal agents used to manage candidiasis belong to four drug classes: azoles, polyenes, echinocandins, and pyrimidine analogs. Azoles and polyenes target the fungal membrane, echinocandins act on the fungal cell wall, and flucytosine impairs nucleic acid synthesis. The selection of antifungal treatment depends on several factors, including the host's immune status, the extent of the infection, previous drug tolerance, and antifungal resistance. Antifungal resistance can be either intrinsic or acquired, with the latter typically occurring after prolonged exposure to antifungal drugs. Resistance mechanisms involve alterations in the binding sites through ERG11 gene mutations, overexpression of efflux pumps (CDR1, CDR2, or MDR1), and amino acid substitutions in the FKS subunits of glucan synthase. The formation of Candida biofilms may contribute to the emergence of resistance, as biofilms reduce the effectiveness of antifungal agents in penetrating and reaching the intended site of action. Researchers have developed novel antifungals that demonstrate activity against Candida species.

Rezafungin : Rezafungin, a novel echinocandin drug currently in Phase 3 development, has a chemical structure that differs slightly from anidulafungin. This modification involves replacing the hemiaminal region at the C5 ornithine position with a choline animal ether. The resulting structural change has provided rezafungin with exceptional stability and enhanced solubility, leading to significantly prolonged pharmacokinetic properties compared to other drugs in its class. This long-acting feature allows for less frequent dosing, which could potentially improve patient compliance, particularly for individuals requiring extended therapy post-hospitalization. Additionally, the extended pharmacokinetic profile of rezafungin holds promise for prophylactic use, an area traditionally dominated by triazole antifungals. Rezafungin, derived from anidulafungin, exhibits potent activity against Candida, Aspergillus, and Pneumocystis, but shows limited efficacy against Cryptococcus species and certain rare molds. Despite the potential for increased MICs due to FKS mutations, rezafungin has demonstrated a 90% success rate in achieving effective drug exposure in group C. With improved tissue absorption and a long half-life of 133 hours in humans, rezafungin can be administered once weekly, thanks to

chemical modifications that reduce degradation. Furthermore, rezafungin exhibits activity against biofilms formed by Candida and Pneumocystis. In murine models, rezafungin is rapidly absorbed and distributed in liver tissue, with a higher distribution in necrotic lesions compared to micafungin. The efficacy of rezafungin was compared to caspofungin in the 2 STRIVE series, showing higher initial exposure (400 mg dose followed by a weekly dose of 200 mg) and faster mycological eradication in five and ten days compared to tocaspofungin. Rasafungin demonstrated non-inferiority to caspofungin in terms of the primary Globalcure endpoint (clinical, radiological, and mycological eradication) and 30-day mortality in patients with candidiasis and/or candidemia. Despite its high frontal exposure, the safety and tolerability profile of rezafungin is similar to other echinocandins. Razafungin remains stable in hepatocytes and does not undergo biotransformation, indicating a low likelihood of drug interactions. Rezafungin is primarily excreted in feces (with only 1% excreted unchanged in urine). No dosage adjustment is necessary for patients with renal or hepatic impairment.

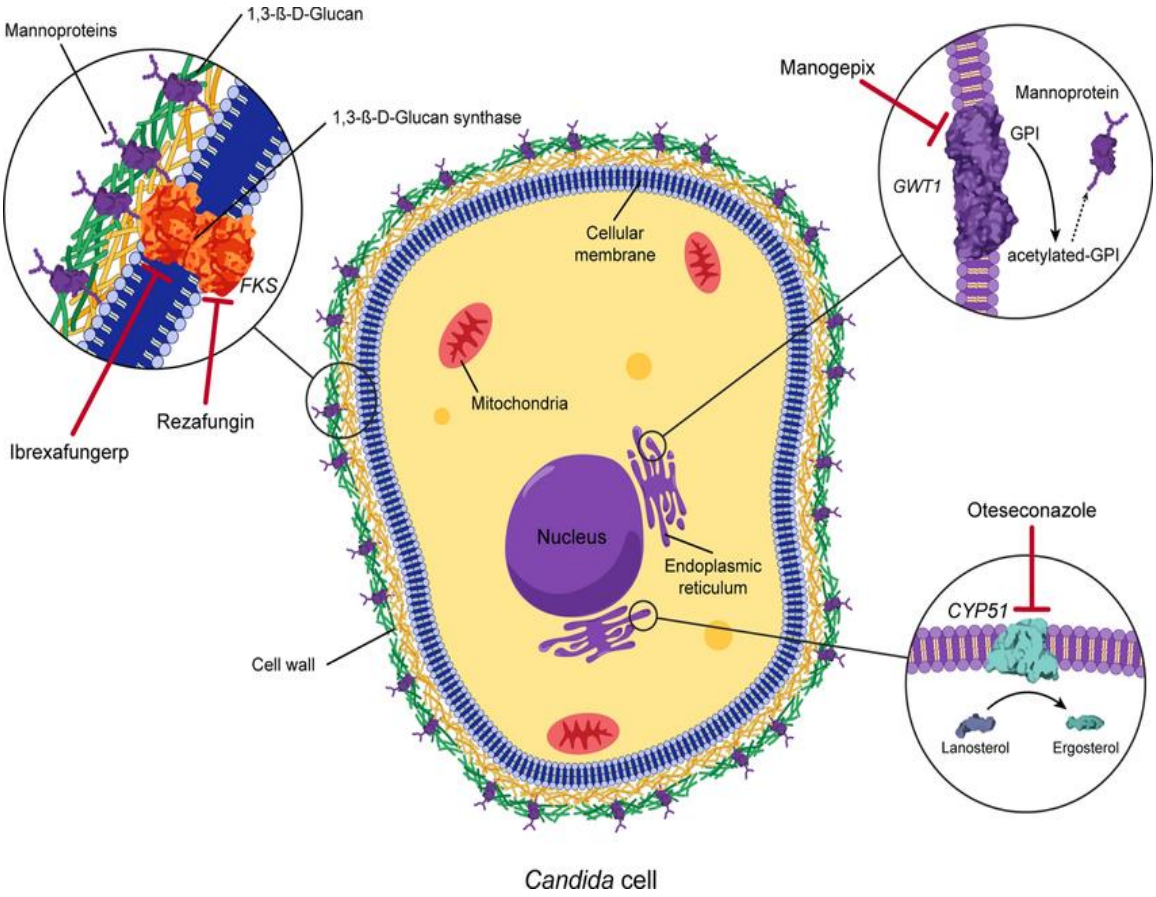

Fig 1 : Candida Cell

The mechanism of action of a new antifungal agent with anticandidal activity. Rezafungin and ibrexafungerp are inhibitors of subunits of the cell wall complex (1,3)-beta-d-glucan synthase. The FKS gene encodes (1,3)-β-d-glucan synthase. Manogepix is the active component of fosmanogepix, it inhibits the fungal acetyltransferase (Gwt1) in the endoplasmic reticulum, inhibits the acetylation of myo-inositol, and inhibits the biosynthesis of glycosylphosphatidylinositol, thereby affecting to the function of mannoprotein. Oticonazole inhibits fungal CYP51, preventing the conversion of lanosterol to ergosterol.

Table 1. In vivo characterization of rezafungin.

Aspects	Animal model	Feature
Pk/pd	Healthy mouse, rat, dog, cynomolgus monkey, chimpanzee; Immunocompetent mouse model of invasive candidiasis; Immunocompetent mouse model of intra-abdominal candidiasis; Neutropenic mouse model of invasive candidiasis	Dose proportional drug exposure (Cmax and AUC); Very long half-life (longer than any of currently approved echinocandin drug); Low clearance and wide tissue distribution; Quick and sustained penetration at infected tissue sites; AUC/MIC is the best index associated with efficacy; The shape of exposure curve also influences efficacy
Efficacy	Neutropenic mouse model of invasive candidiasis; Immunocompetent mouse model of intra-abdominal candidiasis; Immunocompetent rabbit model of invasive candidiasis; Neutropenic mouse model of disseminated invasive aspergillosis; Immunosuppressed mouse model of Pneumocystis pneumonia	Comparable or better efficacy than comparator drug (anidulafungin or micafungin) in Candida infection models, including those caused by echinocandin- and azole-resistant Candida strains; Effective in improving survival and reducing kidney burdens in both azole-sensitive and -resistant Aspergillus infections; Comparable efficacy to the standard of care (TMP/SMX) in prevention of Pneumocystis pneumonia

Clinical Development :

Thus far, rezafungin has progressed to Phase 3 studies. The most updated information of the clinical trials is summarised in Table 2.

Table 2. Summary clinical evaluation of rezafungin

Clinical Status	Trial (ClinicalTrials.gov identifier)	Objective	Key Finding
Phase 1 (completed)	Single-ascending-dose study (NCT02516904) Multiple-ascending-dose study (NCT02551549)	Safety, tolerability, and PK	No safety issues were noted; Dose-proportional plasma exposures (AUC and Cmax) and low clearance; Long half-life (~80 h after first dose and~150 h following addition dose)
Phase 2 (completed)	STRIVE (NCT02734862) RADIANT (NCT02733432)	Efficacy to treat candidemia and invasive candidiasis Efficacy to treat Vulvovaginitis	Rezafungin IV 400 mg first week followed by 200 mg once weekly regimen showedgreater efficacy than caspofung Topical formulations of rezafungin were safe and well tolerated; Cure rates of topical rezafungin were lower than those achieved with fluconazole
Phase 3 (ongoing)	ReSTORE (NCT03667690 ReSPECT (NCT04368559))	Efficacy to treat candidemia and invasive candidiasis Efficacy to prevent invasive fungal infections due to Candida, Aspergillus,and Pneumocystis	To be determined To be determined

The Place of Rezafungin in the Clinical Setting: :

Fungi are the preferred treatment for Candida spp. acute infections when used as a rescue treatment, either alone or in combination with azoles, for various types of aspergillosis. Some studies have also shown the anti-pneumocystis activity of primary echinocandins, as they have demonstrated the ability to target bacteria while sparing trophic bacteria. However, they lack selectivity for Pneumocystis spp. infections. Rezafungin appears to be similar to first-generation echinocandins and can be utilized in similar clinical scenarios. The Restore and Strive clinical trials have consistently shown the efficacy of rezafungin (compared to caspofungin) in treating candidemia and other forms of candidiasis, including as an oral treatment. Furthermore, rezafungin has been utilized in the management of painful and recurrent genital warts (RADIANT study) and in the treatment of Candida spp., Pneumocystis spp., and Aspergillus spp. infections. It has also been investigated for the treatment of fungal diseases in patients undergoing allogeneic blood and marrow transplantation (Respect study). Once approved, rezafungin will broaden the clinical application of echinocandins as both prophylactic and therapeutic options for invasive candidiasis.

Molecular Mechanism of Action of Rezafungin :

Previously mentioned, echinocandins hinder the formation of cell walls, particularly the creation of 1,3-β-D-glucan. The decrease in 1,3-β-D-glucan within the cell wall leads to a modification in cell shape, resulting in osmotic instability, cell death, and/or inhibition. These antifungals function as fungicides against various Candida species, such as Candida albicans, C. dubliniensis, C. krusei, and C. tropicalis. Some Candida species, like the C. parapsilosis complex and Meyerozyma guilliermondii (also known as C. guilliermondii), naturally display polymorphisms in Fksp that affect their susceptibility to echinocandin in vitro, requiring more time and a higher dosage for effectiveness. The drug exhibits a different behavior in vitro, with a maximum bactericidal rate, and certain emerging species like Candida auris show resistance to this drug in vitro.

Preclinical Pharmacokinetic of rizafungin :

Various research groups have explored the pharmacokinetic properties of rezafungin using diverse animal models. In an immunocompetent mouse model of disseminated candidiasis caused by Candida albicans, it was observed that the pharmacokinetics following single intraperitoneal doses of rezafungin ranged significantly from 10 to 60 mg/kg. Drug exposure, as measured by the maximum plasma concentration (Cmax) and the area under the curve (AUC), showed an increase from 23.1, 43.3, 82.3 to 95.8 µg/mL, and 736, 1250, 2380 and 3300 µg*h/mL 48 h, for doses of 10, 20, 40, and 60 mg/kg, respectively. The half-life of the drug ranged from 29.8 to 52.0 hours. Furthermore, the pharmacokinetics of rezafungin were also studied in healthy animals. A study conducted by James and colleagues involved a pharmacokinetic analysis after a single intravenous dose of rezafungin (administered as a 10-minute slow bolus) in healthy beagle dogs, comparing it with anidulafungin. The study revealed that rezafungin exhibited a half-life of 53.1 hours, approximately 5 times longer than the 11.6 hours observed for anidulafungin. Additionally, the volume of distribution was higher for rezafungin (1360 ml/kg) compared to 779 ml/kg for anidulafungin**.** Hence, the clearance rate for rezafungin is 19 mL/h/kg, which is lower compared to anidulafungin (47 mL/h/kg). Subsequently, another study was conducted shortly after the single dose PK study, which expanded the research to include various animal species such as rats, mice, dogs, and non-human primates (cynomolgus monkeys and chimpanzees). The study also included both male and female animals, with different levels of rezafungin administered to rats and mice. As a result, rezafungin exhibited a similar PK profile across all tested species, characterized by low bioavailability, low volume of distribution, and a long half-life (t1/2). The difference in PK between rezafungin (longer t1/2 and higher AUC) and anidulafungin is more prominent at higher doses, particularly in non-human subjects. In another study, matrix-assisted laser desorption/ionization mass spectrometry imaging was utilized to assess the distribution and quantitative levels of rezafungin and micafungin in wound tissue within a mouse model of intra-abdominal candidiasis. Both drugs exhibited accumulation in the lesions and their therapeutic regimens. However, rezafungin accumulated rapidly

and maintained higher levels in the lesions for a longer duration compared to micafungin. This higher level of accumulation was associated with increased death and sterilization. Additionally, the study demonstrated that rezafungin, but not micafungin, caused lesions at a level surpassing the total resistance of the mutant infectious virus. This suggests that rezafungin has the ability to prevent the development of resistance in Candida cells when administered at the appropriate dose. Please refer to Figure 1 for the chemical structures of rezafungin and anidulafungin. The choline amine ether and C5 Ornithine position of rezafungin are highlighted in red. µg*h/mL, respectively, at 48 hours post-dose for 10, 20, 40, and 60 mg/kg. The half-life of rezafungin ranged from 29.8 to 52.0 hours. Furthermore, a pharmacokinetic study in healthy beagle dogs showed that rezafungin has a half-life of 53.1 hours, which is approximately 5 times longer than that of anidulafungin. The rate at which rezafungin is distributed in the body (1360 ml/kg) is higher than that of anidulafungin (779 mg/kg), leading to a lower rate at which rezafungin is cleared from the body (19 ml/h/kg) compared to anidulafungin (47 ml/h/kg). Further research expanded the evaluation of how the body processes these drugs to include various animal species such as mice, rats, dogs, and primates (cynomolgus monkeys and chimpanzees). Additionally, gender differences in rats and mice were taken into account. Rezafungin exhibits similar profiles in terms of how the body processes it, characterized by low clearance, low distribution, and a long half-life (t1/2), regardless of the method of administration. In various animal models, including one involving voice, differences in how the body processes rezafungin and anidulafungin have been observed. This unique pharmacokinetic property of rezafungin distinguishes it from other echinocandins that have been studied traditionally in terms of how the body processes them, allowing for better penetration of the drug into infected tissue sites. A study using Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry imaging examined the spatial distribution and amount of the drug that accumulates in tissue lesions using a mouse model of intra-nasal candidiasis. Both rezafungin and anidulafungin were found to accumulate in the lesions at the therapeutic dose used in humans. However, rezafungin accumulated more quickly and remained in the lesions for a significantly longer time, resulting in higher concentrations compared to the other drug, Micafungin. This higher concentration of the drug was associated with a greater reduction in the amount of Candida cells in the tissue and improved sterilization. Furthermore, the study showed that both drugs were able to penetrate the lesions, whereas Micafungin did not reach levels above the concentration needed to prevent the development of drug-resistant strains. These findings suggest that appropriate dosing of rezafungin may effectively prevent the development of drug resistance in Candida cells..

In Vivo Effectiveness :

Models of Animals :

Rezafungin has demonstrated its efficacy in the treatment of invasive infections caused by various pathogens since its initial in vitro characterization, as supported by a growing body of research. Animal models have observed the presence of fungi such as Candida species, Aspergillus species, and Pneumocystis species. Most studies utilized immunocompromised mice to induce invasive infections caused by different pathogens, except for one study that assessed the effectiveness of a treatment for Candida endophthalmitis using a rabbit model, and another study that examined burden reduction in an intra-abdominal candidiasis mouse model. In longer-term trials, mice were predominantly used, particularly those where survival was the primary outcome. On day 0, fungal strains were intraperitoneally injected into neutropenic mice to induce systemic infection. For experiments with extended durations, such as those involving survival analysis, mice were often treated with two doses of cyclophosphamide at days -4 and -1 prior to infection to deplete neutrophils. Additional doses of cyclophosphamide were administered as necessary to maintain persistent neutropenia. To establish a systemic infection, fungal strains were injected intraperitoneally into neutropenic mice on day zero. Kidney burden was assessed at one or more time intervals, at least 24 hours after infection, using rezafungin, comparator antifungals, and the vehicle control, as specified in each research. These treatments were administered two hours after infection

Expanded Access Use of Rezafungin for Salvage Therapy of Invasive Candida glabrata Infection:
A Case Report- Esophageal perforation complicated the surgical procedure, leading to a transition from oral antifungal medication to intravenous micafungin due to the risk of worsening the perforation. The susceptibility results for the two C. glabrata isolates were taken into account. Various long-term suppressive options were evaluated during the outpatient follow-up in April 2020 because of the presence of retained platinum coils and the potential for a persistent chronic infection with multidrug-resistant C. glabrata. Antifungal susceptibility testing for rezafungin was conducted on an isolate (Isolate 4) from the aortic graft material using the CLSI reference method. Sanger Sequencing was carried out on the FKS1 and FKS2 genes, revealing a D666Y mutation in the FKS2 gene HS1. Informed consent and institutional review board approval were obtained for compassionate use of rezafungin. Intravenous rezafungin was initiated in May 2020 with a loading dose of 400 mg, followed by a weekly maintenance dose of 200 mg, which is still ongoing. The patient did not experience any laboratory abnormalities and only had a transient rash with no clinical toxicities related to rezafungin use. Serial serum β-D-glucan assays remained negative from May 2020 to June 2021, and a repeat chest CT angiogram in October 2020 did not reveal any signs of ongoing infection. A timeline of the patient's clinical progress and antifungal treatment is depicted in Figure 2.

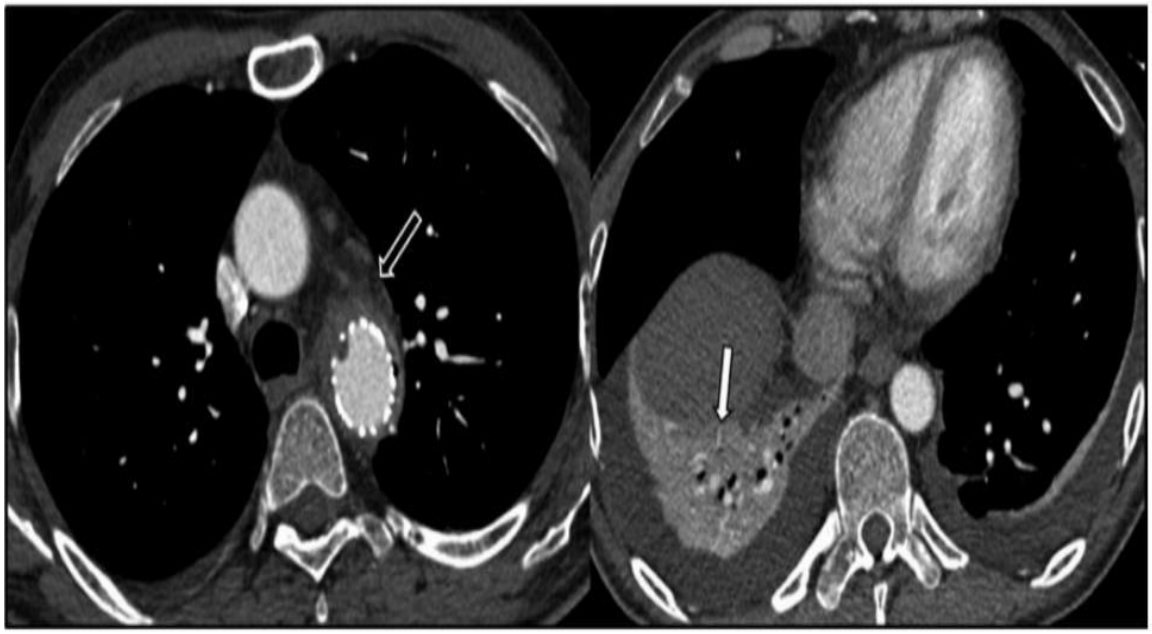

Figure 2. Axial CT angiogram sections below the level of the aortic arch, performed on June 11, 2017. Soft tissue thickening and stranding surrounding the descending thoracic aortic stent graft concerning graft infection (black arrow). There is no mediastinal fluid collection. There is right lower lobe consolidation and/or collapse (white arrow) and small bilateral pleural effusions. Abbreviation: CT, computed tomography.

Chemical structure and structure–activity relationships :
Rezafungin, a cyclic hexapeptide with a lipophilic tail, is an analog of anidulafungin that is characterized by the presence of a choline moiety at the C5 ornithine position. This structural modification of rezafungin has resulted in improved resistance against degradation pathways in the host and the absence of reactive intermediates that could potentially cause harm. Despite these distinctions, rezafungin demonstrates comparable potency and range of activity to other echinocandins in laboratory settings. Further investigations into biotransformation have

revealed that rezafungin remains stable in liver microsomes (in rats, monkeys, and humans) as well as hepatocytes (in rats, monkeys, dogs, and humans).

Stability and solubility:

Stability and solubility were assessed by conducting experiments using various matrices such as rat, dog, monkey, and human plasma. The objective was to determine the physical stability of rezafungin and anidulafungin after incubation for 44 hours at 37 °C. The results revealed that rezafungin exhibited significantly higher stability (ranging from 79% to 94%) compared to anidulafungin (ranging from 7% to 15%) after the specified incubation period. Moreover, when incubated in phosphate-buffered saline at 37 °C, rezafungin demonstrated superior stability (96%) in comparison to anidulafungin (42%). Additionally, rezafungin displayed minimal degradation when subjected to long-term storage at high temperature (40 °C) as a lyophilized powder, or when stored at room temperature in 5% dextrose (for 15 months), 0.9% saline (for 12 months), or sterile water (for 18 months)

Microbiological susceptibility :

Several surveillance studies have assessed Rezafungin's susceptibility to both wild-type and antifungal-resistant isolates. Despite varying resistance patterns, Rezafungin's minimum inhibitory concentrations (MICs) against Candida and Aspergillus were found to be similar to those of comparator echinocandins. Furthermore, it was proven that Rezafungin's effectiveness was comparable to that of other echinocandins. In vitro studies revealed that Rezafungin and micafungin displayed a typical echinocandin pattern when tested against isolates with FKS mutation and wild-type C. albicans and C. glabrata, inhibiting glucan synthase. Notably, one C. glabrata (MIC = 1 μg/mL) and one C. albicans (MIC = 0.25 μg/mL) with F626S and S645P mutations in FKS1, respectively, exhibited elevated MICs. Additionally, a brief study was conducted on 14 ATCC strains.

Animal safety and efficacy :

Rats were utilized to assess the safety of high-dose rezafungin and an equivalent dosage of anidulafungin. Non-infected rats tolerated rezafungin well, showing no effects on body weight, coagulation, haematology, or urinalysis. Conversely, high-dose anidulafungin administration resulted in reduced body weight, adverse changes in coagulation and haematological parameters, and dysfunction in the liver and spleen. Reactive metabolites, absent in rats given rezafungin, were produced in rats given anidulafungin, as evidenced by a glutathione trapping experiment. This discovery suggests that the toxicities associated with high doses of anidulafungin may be due to the accumulation of these metabolites. When CD-1 mice infected with Candida albicans were treated with rezafungin at levels comparable to anidulafungin, the fungal kidney burden decreased in a dose-dependent manner. A subsequent study validated these results by comparing wild-type and resistant FKS mutant C. albicans strains. Rezafungin, at humanized doses, proved more effective than micafungin in reducing the fungal kidney burden for both wild-type and FKS mutant strains. Furthermore, rezafungin exhibited fungicidal properties in a murine disseminated infection model with azole-resistant C. albicans. In neutropenic mice infected with C. albicans or Aspergillus fumigatus, rezafungin demonstrated favorable outcomes similar to anidulafungin. Additionally, rezafungin was effective in a mouse model of disseminated aspergillosis. Finally, rezafungin showed comparable efficacy to trimethoprim/sulfamethoxazole in preventing the development of Pneumocystis pneumonia by inhibiting the formation of both trophic and cyst/asci reproductive forms of Pneumocystis murina in an immunocompromised murine model

Phase 1 pharmacokinetics in healthy humans :

Rezafungin underwent evaluation in two phase 2 trials involving healthy volunteers to assess the safety and pharmacokinetics of various dosage regimens. These trials consisted of a single-ascending dose study with 32 participants and a multiple-ascending dose study with 24 participants. The dosage regimens ranged from 50 mg to 400 mg. In the single-ascending dose study, the participants were divided into four dose groups (50, 100, 200, and 400 mg), each comprising eight subjects. The multiple-ascending dose study included three dose groups (100

mg × 2 doses, 200 mg × 2 doses, and 400 mg × 3 doses), with eight subjects in each group. Rezafungin was administered to all groups via a 1-hour infusion. The majority of participants were White (88–97%), with an age range of 43–46 years and a mean body mass index (BMI) of 27.2–28.1 kg/m2. The pharmacokinetic data can be found in Table 2. Rezafungin demonstrated consistent plasma exposure across the dosage range of 50–400 mg, a long half-life (>80 hours), and minimal excretion in urine (<0.5%). The maximum plasma concentration (Cmax) values ranged from 5–6 μg/mL at the 100 mg dose to 22–30 μg/mL at the 400 mg dose. Throughout the study period, which included electrocardiogram, haematology, and serum chemistry assessments, no safety concerns were identified. There were no reports of serious or severe adverse events, and none of the participants discontinued the trials due to adverse effects. All adverse events resolved completely before the conclusion of the study. Some participants experienced mild transient infusion reactions, such as flushing, nausea, and chest tightness, after receiving the third 400 mg dose in the multiple-ascending dose study, but no interruptions in dosing occurred.

Tablet 3 :Human pharmacokinetics of rezafungin: results from two phase 1 single-dose and multiple-dose studies [33].

Study	Single dose	Multidose, Day 1	Multidose, Day 8	Single dose	Multidose, Day 1	Multidose, Day 8
Dose (mg)	100	100	100	200	200	200
Cmax (μg/mL)	4.86 ± 0.56	5.67 ± 0.89	6.49 ± 0.65	10.9 ± 2.17	10.6 ± 1.93	30.5 ± 13.1
AUC0–168 (μg·h/mL	254 ± 22.9	299 ± 27.4	390 ± 44.1	592 ± 66.8	570 ± 125	813 ± 225
t1/2 (h)	146 ± 3.82	79.1 ± 4.04	158 ± 15.5	125 ± 13.0	81.3 ± 4.30	140 ± 13.2
CL (L/h)	0.240 ± 0.02	0.258 ± 0.02	0.149 ± 0.02	0.219 ± 0.02	0.279 ± 0.07	0.155 ± 0.04
Vss (L)	42.9 ± 4.07	28.8 ± 3.59	29.3 ± 3.70	34.4 ± 4.99	31.7 ± 7.72	28.5 ± 7.18
Vz (L)	50.6 ± 4.96	29.5 ± 3.23	33.8 ± 4.34	39.7 ± 6.99	32.8 ± 9.18	30.9 ± 7.35

The results of the phase 1 studies along with MIC susceptibility data and body mass distribution were used to make a population pharmacokinetic model of rezafungin. Using Monte Carlo simulations and randomly assigned MICs, a single rezafungin 40 mg dose achieved a probability of target attainment of >99% for Weeks 1–3 and >95% for Week 4.

Human safety and efficacy :

The phase 2 study of rezafungin, a drug for candidaemia and invasive candidiasis, was initiated based on the strong results obtained from pre-clinical, animal, and phase 1 studies. This study is designed as a multi-centred, randomised, double-blind trial. The primary endpoint of the study will be the assessment of mycological

eradication and clinical response at Day 14, along with monitoring treatment-emergent adverse events from Days 45 to 59. Two different doses of rezafungin will be evaluated. Both groups will receive an initial dose of rezafungin 400 mg on Day 1, followed by a second dose on Day 8 of either 400 mg or 200 mg. If necessary, a third and fourth weekly dose may be administered to both groups. The results obtained from the group receiving rezafungin will be compared to those from patients receiving caspofungin, who will be given a loading dose of 70 mg followed by 50 mg once daily for 3 days.

Tablet 4 : Summary characterisation of rezafungin.

Area	Feature
Medical chemistry	Echinocandin is structurally differentiated by the C5 ornithine position that confers increased stability and longer half-life.
In vitro susceptibility	Activity against Candida and Aspergillus spp. similar to that of comparator echinocandins.
Resistance Development	Low likelihood of resistance development, as with other echinocandins. Unlike other echinocandins, high plasma drug exposure and safety margin of rezafungin may allow dosing towards the MPC to prevent resistance development.
Safety	Well tolerated in animal models and phase 1 studies in healthy volunteers; wide safety margin that enables high, front-loaded dosing. No dose-limiting hepatotoxicity. Low to no drug–drug interaction potential. No dosage adjustment expected.
Efficacy	Effective in Candida and Aspergillus models, including treatment of less-susceptible Candida and resistant FKS mutant Candida strains. Effective in prevention of Pneumocystis pneumonia (PCP). Significant target tissue penetration. Currently in phase 2 of development.
Pharmacokinetic	Notable pharmacokinetics include high plasma drug exposure that supports front-loaded dosing and long-half-life (≥80 h in humans) allowing once-weekly administration.

Conclusion :

Rezafungin, a novel echinocandin, exhibits a longer PK profile compared to other drugs in its class. Supported by robust preclinical evidence from animal models and promising outcomes from the Phase 2 STRIVE study, Rezafungin is now undergoing two Phase 3 clinical trials to assess its efficacy as an intravenous therapy for the treatment of candidemia and invasive candidiasis, as well as its potential to prevent invasiveness against infections caused by sexually transmitted fungi such as Candida spp., Aspergillus spp., and Pneumocystis spp. With its potent antifungal activity and distinctive pharmacological properties, Rezafungin holds the promise of becoming a first-line treatment and prevention option for invasive fungal infections, surpassing the current standard of care.

Reference :

1. https://pubmed.ncbi.nlm.nih.gov/33438477/
2. Lamoth F, Lockhart SR, Berkow EL, Calandra T. Changes in the epidemiological landscape of invasive candidiasis. J Antimicrob Chemother. 2018;73:i4–i13. doi:10.1093/jac/dkx444
3. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1–e50. doi:10.1093/cid/civ933
4. . Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323–2329. doi:10.1001/jama.2009.1754
5. McCarthy MW, Kontoyiannis DP, Cornely OA, Perfect JR, Walsh TJ. Novel agents and drug targets to meet the challenges of resistant fungi. J Infect Dis. 2017;216:S474–S483. doi:10.1093/infdis/jix130
6. Tortorano AM, Prigitano A, Morroni G, Brescini L,Barchiesi F. Candidemia: evolution of drug resistance andnovel therapeutic approaches. Infect Drug Resist. 2021;14:5543–53. https://doi.org/10.2147/IDR.S274872.
7. Lepak AJ, Zhao M, Andes DR. Pharmacodynamic evalution of rezafungin (CD101) against Candida auris in the Neu-tropenic Mouse Invasive Candidiasis Model. Antimicrob Agents Chemother. 2018;62(11):e01572. https://doi.org/10. 1128/AAC.01572-18.
8. Pfaller MA, Carvalhaes C, Messer SA, Rhomberg PR, Castanheira M. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary invasive fungal isolates (SENTRY Program, 2016 to 2018). Antimicrob Agents Chemother. 2020;64(4):e00099. https://doi.org/10.1128/AAC.00099-20.
9. Bader JC, Lakota EA, Flanagan S, Ong V, Sandison T, Rubino CM, et al. Overcoming the resistance hurdle: pharmacokinetic-pharmacodynamic target attainment analyses for rezafungin (CD101) against Candida albicans and Candida glabrata. Antimicrob Agents Chemother.2018;62(6):e02614. https://doi.org/10.1128/AAC.02614-17.
10. Chandra J, Ghannoum MA. CD101, a novel echinocandin, possesses potent antibiofilm activity against early and mature Candida albicans biofilms. Antimicrob Agents Chemother. 2018;62(2):e01750. https://doi.org/10.1128/ AAC.01750-17.
11. Zhao Y, Prideaux B, Nagasaki Y, Lee MH, Chen PY, Blanc L, et al. Unraveling drug penetration of echinocandin anti- fungals at the site of infection in an intra-abdominal abscess model. Antimicrob Agents Chemother. 2017;61(10):e01009. https://doi.org/10.1128/AAC.01009- 17.
12. https://pubmed.ncbi.nlm.nih.gov/32998224/
13. Sandison, T.; Ong, V.; Lee, J.; Thye, D. Safety and Pharmacokinetics of CD101 IV, a Novel Echinocandin, in Healthy Adults. Antimicrob. Agents Chemother. 2017, 61. [CrossRef] [PubMed]
14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7711656/
15. Zhao, Y.; Perez, W.B.; Jiménez-Ortigosa, C.; Hough, G.; Locke, J.B.; Ong, V.; Bartizal, K.; Perlin, D.S. CD101: A novel long-acting echinocandin. Cell. Microbiol. 2016, 18, 1308–1316. [CrossRef] [PubMed]
16. Ong, V.; James, K.D.; Smith, S.; Krishnan, B.R. Pharmacokinetics of the Novel Echinocandin CD101 in Multiple Animal Species. Antimicrob. Agents Chemother. 2017, 61. [CrossRef]
17. James, K.D.; Laudeman, C.P.; Malkar, N.B.; Krishnan, R.; Polowy, K. Structure-Activity Relationships of a Series of Echinocandins and the Discovery of CD101, a Highly Stable and Soluble Echinocandin with Distinctive Pharmacokinetic Properties. Antimicrob. Agents Chemother. 2017, 61. [CrossRef] [PubMed]
18. Zhao, Y.; Prideaux, B.; Nagasaki, Y.; Lee, M.H.; Chen, P.Y.; Blanc, L.; Ho, H.; Clancy, C.J.; Nguyen, M.H.; Dartois, V.; et al. Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model. Antimicrob. Agents Chemother. 2017, 61, e01009-17. [CrossRef
19. Ong, V.; Ashbaugh, A.; Cushion, M.T. Rezafungin Prevention of

20. Pneumocystis Pneumonia and Pneumocystis Reactivation Using Different Doses and Durations of Prophylaxis in a Mouse Model. Biol. Blood Marrow Transplant. 2020, 26, S328–S329. [CrossRef]
21. Miesel, L.; Lin, K.Y.; Ong, V. Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy. Pharmacol. Res. Perspect. 2019, 7, e00546. [CrossRef] [PubMed
22. B.R. Krishnan, K.D. James, K. Polowy, B.J. Bryant, A. Vaidya, S. Smith, et al. CD101, a novel echinocandin with exceptional stability properties and enhanced aqueous solubility J Antibiot (Tokyo), 70 (2017), pp. 130-135
23. V. Ong, G. Hough, M. Schlosser, K. Bartizal, J.M. Balkovec, K.D. James, et al. Preclinical evaluation of the stability, safety, and efficacy of CD101, a novel echinocandin Antimicrob Agents Chemother, 60 (2016), pp. 6872-6879
24. B.R. Krishnan, K.D. James, K. Polowy, B.J. Bryant, A. Vaidya, S. Smith, et al. CD101, a novel echinocandin with exceptional stability properties and enhanced aqueous solubility J Antibiot (Tokyo), 70 (2017), pp. 130-135
25. M.A. Pfaller, S.A. Messer, P.R. Rhomberg, M. Castanheira Activity of a long-acting echinocandin (CD101) and seven comparator antifungal agents tested against a global collection of contemporary invasive fungal isolates in the SENTRY (2014) Antifungal Surveillance Program Antimicrob Agents Chemother, 61 (2017) pii: e02045-16
26. Y. Zhao, W.B. Perez, C. Jiménez-Ortigosa, G. Hough, J.B. Locke, V. Ong, et al. CD101: a novel long-acting echinocandin Cell Microbiol, 18 (2016), pp. 1308-1316
27. V. Ong, G. Hough, M. Schlosser, K. Bartizal, J.M. Balkovec, K.D. James, et al. Preclinical evaluation of the stability, safety, and efficacy of CD101, a novel echinocandinbAntimicrob Agents Chemother, 60 (2016), pp. 6872-6879
28. K.D. James, C.P. Laudeman, N.B. Malkar, R. Krishnan, K. Polowy Structure–activity relationships of a series of echinocandins and the discovery of CD101, a highly stable and soluble echinocandin with distinctive pharmacokinetic properties Antimicrob Agents Chemother, 61 (2016) e01541-16